UPDATE ON THE MANAGEMENT OF HCV 2016

Screening Diagnosis & Treatment

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I have the following financial relationships to disclose:

- Consultant for: Gilead, Abbvie, Merck
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- Grant/Research Support from: Gilead, Abbvie, Merck
- Stockholder in: None

I will discuss the following off label use and/or investigational use in my presentation:

- SURVEYOR-I and -II: SVR12 (ITT) With ABT-493 + ABT-530 ± RBV (Abbvie research trial not FDA approved)

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Hepatitis C
The Most Deadly Infectious Disease in America

The most deadly infectious disease in America today

Hepatitis C now kills more people in the United States than every other infectious disease combined, according to new government data. The report from the Centers for Disease Control and Prevention found that deaths associated with hepatitis C reached an all-time high of 19,659 in 2014, surpassing the total combined number of deaths from 60 other infectious diseases reported to CDC, including HIV, pneumococcal disease, and tuberculosis.

By Ashley Welch CBS News May 4, 2016, 3:17 PM
By 2007, Deaths From HCV Surpassed Those From HIV

Change in Mortality Rates From 1999 to 2007

HIV
Hepatitis C
Hepatitis B

Hepatitis C: The Silent Epidemic

The Washington Post

By Douglas Dieterich, M.D.
HCV is Nearly 4 Times as Prevalent as HIV and HBV

Prevalence of Chronic Viral Infections

- **HIV**: 1.1 Million\(^1\)
  - 21% Unaware of Infection
- **HBV**: ~800,000 to 1.4 Million\(^1\)
  - 65% Unaware of Infection
- **HCV**: 2.7 to 5 Million\(^1\)
  - 75% Unaware of Infection

- **A 2011 study estimated that as many as 5.2 million persons are living with HCV in the United States**\(^2\)

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HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

3. Gish Hepatology 2015
An Estimated 50% of Chronic HCV-Infected Individuals in the United States are Unaware of Their Infection

Cascade of Care Determined from Systematic Review of Articles Published between 2003 and 2013

Based on available estimates, only a fraction of diagnosed patients have been treated over the last few years.\(^1,2\)

The CDC Recommends Testing all At-Risk Individuals for HCV\(^3\)

HCV = hepatitis C virus; RNA = ribonucleic acid.

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans

Global Distribution and Prevalence of HCV Genotypes: US Focus on GT 1

Identifying Patients with Hepatitis C

• 4-5 million people in the US have hepatitis C virus (HCV) infection

• Most were infected in 1960’s through 1980’s
  – Up to 250,000 cases per year in 1980’s
  – About 50% infected via IDU, rest from blood transfusions, sex, tattoos, medical procedures, and other factors

• Up to 50-75% of people have not been diagnosed

• Risk-based screening misses many people
  – Stigma associated with IDU, even if decades ago

Chronic HCV Infection: Effects on the Liver

Hepatitis C is a leading cause of cirrhosis, hepatocellular cancer, and liver transplants in the United States\(^1-3\)

- **Hepatocellular carcinoma**
  - Age-adjusted incidence has tripled since early 1980s\(^1\)
  - 50% to 60% of HCC patients are infected with HCV\(^1\)
  - Fastest-growing cause of cancer-related deaths\(^4\)

- **Liver transplants**
  - HCV is the most common indication for adult liver transplants\(^2,4\)
  - HCV as the primary cause of disease accounts for 30.1% of adults waiting for a liver transplant\(^2\)

HCC, hepatocellular carcinoma.

Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer as well as Systemic Disease: DM, Renal Disease, Lymphoma and other problems

**Fibrosis**
- Chronic HCV infection can lead to the development of fibrous scar tissue within the liver

**Cirrhosis**
- Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure

**Hepatocellular Carcinoma** (with cirrhosis)
- Cancer of the liver can develop after years of chronic HCV infection

Decompensated cirrhosis:
- Ascites
- Bleeding gastroesophageal varices
- Hepatic encephalopathy
- Jaundice

Chronic liver disease includes fibrosis, cirrhosis, and hepatic decompensation; HCC=hepatocellular carcinoma.
Chronic HCV Infection Affects Many Sites Beyond the Liver

- Neurological (e.g. cognitive impairment)
- Cardiovascular Diseases (CAD)
- Metabolic (e.g. diabetes)
- Immune Complex (e.g. cryoglobulinemic)
- Pulmonary fibrosis
- Renal (e.g. glomerulonephritis)
- Lymphoproliferative (e.g. B cell lymphoma)
- Dermatological (e.g. porphyria cutanea tarda)
Natural History of HCV Infection

Exposure (Acute Phase)
- 15% Resolved
- 85% Chronic

Cirrhosis
- 20% progression rate accelerated with HIV, HBV, alcohol

- 5-year survival in patients with HCC is <5%2

Time (yr)
- 10
- 20
- 30

ESLD = end-stage liver disease
HCC = hepatocellular carcinoma
In a prospective, observational longitudinal study of 9,783 US patients with chronic HCV infection, nearly 30% developed cirrhosis.

Characteristics associated with cirrhosis include:

- Age >40 years
- Male sex
- Hispanic ethnicity
- HIV coinfection
- History of alcohol abuse

HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Disease Progression With Chronic HCV Infection

Proportion of Chronic HCV Patients Progressing to Decompensation or HCC Over a Mean of 5 Years

HCC = hepatocellular carcinoma; HCV = hepatitis C virus; F2 = portal fibrosis with few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis.

Predictors of Virologic Response

Viral Factors
- Genotype
- Viral Load

Host Factors
- Age
- Cirrhosis
- Race
- Gender
- Weight
- Hepatic Fe Overload
- Coinfection (HIV, HBV)
- Steatosis
- Hyperinsulinemia

HCV Can Now Be Cured in Most Patients

- Unlike HIV and HBV infection, HCV infection is a curable disease
  - HCV does not archive its genome
- What does cure mean?
  - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  - SVR12 is almost invariably durable

Efficient Identification of Patients with HCV

50 million “risk identified” or ~80 million 1945-1965 cohort who need to be tested for HCV in US

4 -5 million people with HCV in US

25% diagnosed with HCV

Treatment and Management

Improve Diagnosis

1Tomaszewski Am J Public Health 2012; 102 (11):e101
### CDC Recommendations

- Everyone born from 1945 through 1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels.
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV positive persons

### USPSTF Grade B Recs*

- Everyone born from 1945 through 1965 (one-time)
- Past or present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

*Only pertains to persons with normal liver enzymes; if elevated liver enzymes need HBV and HCV testing

Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US¹

An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)³

CDC and USPSTF Recommendations for HCV Screening

• Regardless of risk factors, one-time testing for HCV of adults born between 1945–1965\textsuperscript{1,2}
  – Testing of persons of all ages at risk for HCV infection

• CDC also recommends for those identified with HCV infection\textsuperscript{1}
  – Brief alcohol screening and intervention as clinically indicated
  – Referral to appropriate care and treatment services for HCV infection and related conditions

Initial Hepatitis C Testing and Evaluation

Who Should Be Tested for Hepatitis C?

New: Anyone born between 1945 and 1965 should be tested once, regardless of risk factors

In addition, patients with the following risk factors:
- Elevated ALT (even intermittently)
- A history of illicit injection drug use or intranasal cocaine use (even once)
- Needle stick or mucosal exposure to blood
- Current sexual partners of HCV infected persons
- Received blood/organs before 1992
- Received clotting factors made before 1987
- Chronic hemodialysis
- Infection with HIV
- Children born to HCV-infected mothers

Why Test People Born Between 1945-1965?

- 76% of the ~4 million people with HCV infection in the US are baby boomers
- In the 1945-1965 cohort:
  - All: 1 out of 30
  - Men: 1 out of 23
  - African American men: 1 out of 12
- Up to 75% do not know they have HCV
- 73% of HCV-related deaths are in baby boomers

What Can Happen to People with Hepatitis C?

- It is important to identify if patients have cirrhosis
- Patients with cirrhosis are at risk for liver cancer (HCC) and liver decompensation (ascites, variceal bleed, hepatic encephalopathy, jaundice)
- Hepatitis C is curable, and cure reduces the risk of severe complications, even with cirrhosis
- Refer patients to a specialist who has

<table>
<thead>
<tr>
<th>Hepatitis C Antibody (HCV Ab)</th>
<th>Negative (-)</th>
</tr>
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<tbody>
<tr>
<td>Positive (+)</td>
<td></td>
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Check HCV RNA (viral load)

<table>
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<tr>
<th>Positive (+)</th>
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</table>

Hepatitis C infection

Evaluation and referral

STOP here if no concern for acute infection or severe immunosuppression. If so, check HCV RNA.

These people are NOT chronically infected.
- Detectable HCV Ab with negative HCV RNA can occur with spontaneous clearance of infection (about 25% of people exposed to HCV will clear; verify HCV RNA negative in 4 to 6 months) or with treatment of HCV.

Example ICD-9 codes for HCV antibody testing:
- V73.89: screening for other specified viral disease
- 790.4: nonspecific elevation of levels of transaminase; use if patient ever had an elevated ALT

Counsel Patients with HCV Infection About Reducing Risk of Transmission

- Do not donate blood, body organs, other tissue, or semen
- Do not share personal items that might have small amounts of blood (toothbrushes, razors, nail-grooming equipment, needles) and cover cuts and wounds
- HCV is not spread by hugging, kissing, food or water, sharing utensils, or casual contact
- If in short term or multiple relationships, use latex condoms. No condom use is recommended for long-term monogamous couples (risk of transmission is very low)

Initial Management

- Evaluate alcohol use (CAGE, AUDIT-C) and recommend stopping use
- Vaccinate for hepatitis A and hepatitis B if not previously exposed
- Evaluate sources of support (social, emotional, financial) needed for HCV treatment

HCV Antibody Test Volume Increased after EMR Prompt

Average = 303 tests/4 weeks

Average = 438 tests/4 weeks

Average = 1192 tests/4 weeks

CDC 1945-1965 testing guidelines

EMR prompt

Beth Israel Deaconess Medical Center, Boston, MA, Quality Outcomes Data, 6/5/14
PCP Education Example: Screening in Clinic

1,000 adult patients → 330 baby boomers → 10 HCV antibody positive → 7 HCV RNA positive → 3 with more advanced fibrosis

4 with mild fibrosis

Efficiently identify birth cohort 1945-1965:
- Electronic prompt

~1/3 of adults are in 1945-1965 cohort
- 1 of 30 baby boomers
- 1 of 23 men baby boomers
- 1 of 12 African American men baby boomers
- 15%-30% of HCV antibody patients will spontaneously clear
- Up to 25% of baby boomers may have cirrhosis
- 75% of cirrhotic patients are men

Davis, Gastro 2010; 138: 513
Screening of Baby Boomers May Prevent >120,000 Deaths Due to HCV Infection

- Birth-cohort screening in primary care would identify 86% of all undiagnosed cases in the birth cohort, compared with 21% under risk based screening\(^1\)
- Cost effectiveness of HCV screening is comparable to cervical cancer or cholesterol screening (cost/QALY gained with protease inhibitor+IFN+RBV = $35,700)

Markov chain Monte Carlo simulation model of prevalence of hepatitis C antibody stratified by age, sex, race/ethnicity, history of injection drug use, and natural history of chronic hepatitis C.

PCP Barriers at CareGroup

• Recommendations to test everyone born from 1945 - 1965 means testing too many people and this is too expensive
• There is no need to screen since clinicians can identify people who have clinically significant liver disease by their clinical presentation and will test for HCV at that point
• Patients will die with their HCV, not of it, and a lot of patients will be upset/harmed by this testing in an effort to identify the few who will actually develop significant disease
• There is nothing to do for HCV (if not aware that HCV is potentially curable) or, the treatment is more toxic than the disease
• Everybody with anti-HCV antibody seropositivity has active HCV infection
• There are too many electronic medical records prompts already and any more will overwhelm clinicians
TREATMENT
HCV Lifecycle

1. Receptor binding and endocytosis
2. Fusion and uncoating
3. (+) RNA
4. Translation and polyprotein processing
5. RNA replication
6. Membranous web
7. Virion assembly
8. Transport and release
HCV Genotype 1 Is Most Common in the United States

Estimated Prevalence of HCV GTs in the United States

- 46% GT1a
- 26% GT1b
- 11% GT2
- 9% GT3
- 6% GT4
- 2% GT5, 6, or other

- HCV infection is differentiated into 6 major viral genotypes, which have nucleotide sequences that differ by 30%–35%.
- Approximately 72% of HCV infections in the United States are GT1

HCV = hepatitis C virus; GT = genotype.
## Summary of Direct-Acting Antivirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbreviation</th>
<th>Class</th>
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</thead>
<tbody>
<tr>
<td>ABT-493</td>
<td>ABT-493</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>ABT-530</td>
<td>ABT-530</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>DCV</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>DSV</td>
<td>NS5B nonnucleoside polymerase inhibitor</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>EBR</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>GZR</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>GS-9451</td>
<td>-</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>GS-9669</td>
<td>-</td>
<td>NS5B nonnucleoside polymerase inhibitor</td>
</tr>
<tr>
<td>GS-9857</td>
<td>-</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>LDV</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>OBV</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>PTV</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>SMV</td>
<td>NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>SOF</td>
<td>NS5B nucleotide polymerase inhibitor</td>
</tr>
<tr>
<td>Velpatasvir (formerly GS-5816)</td>
<td>VEL</td>
<td>NS5A inhibitor</td>
</tr>
</tbody>
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Slide credit: clinicaloptions.com
REAL-WORLD EXPERIENCE: 
HCV-TARGET AND TRIO NETWORK

- HCV treatment regimen was selected and administered at clinicians’ discretion according to local standards of care
- The HCV-TARGET and TRIO Network studies were supported by Gilead Sciences, Inc. Real-world experience data were derived from patient medical records and specialty pharmacy databases. Such data are retrospective and observational in nature, and are not based on controlled clinical studies. Results from these cohorts may differ from results seen in the clinical practice of a particular provider

\(^a\)Patients in this analysis completed treatment before July 1, 2015.  
\(^b\)In this analysis, all patients initiated therapy between October 2014 and March 2015.  
HCV-TARGET: SVR12 With 8-, 12-, or 24-Wk Ledipasvir/Sofosbuvir ± Ribavirin

- Only 131 out of 323 pts who qualified for 8-wk treatment (treatment naive, no cirrhosis, and baseline HCV RNA ≤ 6 million IU/mL) received 8-wk regimen.

<table>
<thead>
<tr>
<th>Wks of Treatment</th>
<th>LDV/SOF 8 Wks (n = 131)</th>
<th>LDV/SOF 12 Wks (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12, %</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Failure, %</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>SVR12 according to Wk 4 HCV RNA, % (n/N)</td>
<td>(n = 99)</td>
<td>(n = 133)</td>
</tr>
<tr>
<td>Below limit of quantification</td>
<td>97 (89/92)</td>
<td>97 (114/117)</td>
</tr>
<tr>
<td>Quantifiable</td>
<td>100 (7/7)</td>
<td>94 (15/16)</td>
</tr>
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</table>

Slide credit: clinicaloptions.com
ASTRAL-1: Sofosbuvir/Velpatasvir for GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial (N = 740), tx naive or experienced
  - Pts randomized 5:1 to sofosbuvir/velpatasvir or placebo for 12 wks
  - Key baseline characteristics: cirrhosis 19%, tx exp’d 32%, BL NS5A RAVs 42%
- No impact of cirrhosis, tx experience, BL NS5A RAVs on SVR12 rates

Potential Future HCV Therapies
SURVEYOR-I and -II: SVR12 (ITT) With ABT-493 + ABT-530 ± RBV

- GT1 or 2: SVR12 achieved by all pts with BL NS3 or NS5A resistance
- Most AEs mild, most frequent AEs fatigue, nausea, diarrhea, headache
  - For GT1 and 2: no tx-related serious AEs, no discontinuations for AE

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<tr>
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<tbody>
<tr>
<td>ABT-493 200 mg</td>
<td>97</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>ABT-530 120 mg</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>RBV 200 mg</td>
<td>100</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>ABT-493 40 mg</td>
<td>38*</td>
<td>24†</td>
<td>28/30</td>
</tr>
<tr>
<td>ABT-530 120 mg</td>
<td>40/40</td>
<td>24/24</td>
<td>28/30</td>
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<tr>
<td>RBV 120 mg</td>
<td>25/25</td>
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<tr>
<td>RBV 120 mg</td>
<td>25/25</td>
<td>25/25</td>
<td>30/30</td>
</tr>
</tbody>
</table>

*Viral relapse in 1 pt with GT1a HCV; NS5A Q30K + H58D emerged at relapse. †1 pt lost to follow-up after 2-wk Tx.


Slide credit: clinicaloptions.com
HCC Screening Guidelines

- EASL-EORTC Guidelines 2012\textsuperscript{[1]}: “\textit{Pts at high risk for developing HCC should be entered into surveillance programs. Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 mos}”
  - High risk: cirrhosis CP A, B, or C (awaiting LT for CP C); noncirrhotic HBV carriers with active hepatitis or family HCC history; noncirrhotic pts with HCV and F3 fibrosis

- AASLD/IDSA HCV Guidance 2016\textsuperscript{[2]}: “\textit{Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for pts with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR}”

Treatment Overall Conclusions:

- Highly active area of drug development with multiple treatment options available now and more expected in the near term
- All oral regimens offer very favorable safety profiles and SVR rates >90%
- HIV/HCV infected patients recommended regimens are the same as for HCV monoinfected patients; however, extra caution needed regarding drug:drug interactions
- AASLD/IDSA Guidance Document
  - Watch for updates (www.hcvguidelines.org)
- Drug:drug interactions reference
  - www.hep-druginteractions.org
  - Smartphone App HEP iChart (Liverpool, England)
SVR Was Associated with Improved Quality of Life in a Real-World Clinic Population

A study of community patients from hospitals in Vancouver has shown that sustained responders reported higher scores than treatment failures on each domain of the SF-36 and on utility measures.

Mean difference in scores (SVR versus treatment failure)

This analysis was part of a larger study examining the quality of life and economic burden of HCV in community patients recruited from 5 clinical settings in Vancouver, British Columbia, and included a cross-sectional administration of questionnaires with retrospective review of medical records. (133 responders and 102 treatment failures) completed questionnaires at an average of 3.7 years after end of treatment. Patients with advanced liver disease were excluded.

Sustained responders = undetectable HCV viral levels 6 months after therapy; treatment failures = detectable HCV viremia after therapy, or patients with an end-of-treatment response who relapsed.

MCS = mental summary score (0-100); PCS = physical summary score (0-100). *P<.0001; †P<.001; ≠P<.01.

SVR Reduced Risk of All-Cause Mortality in a Retrospective VA Study

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=12,166)</td>
<td>(n=2904)</td>
<td>(n=1794)</td>
</tr>
<tr>
<td>SVR rate: 35%</td>
<td>SVR rate: 72%</td>
<td>SVR rate: 62%</td>
</tr>
</tbody>
</table>

Cumulative Mortality (%)

Retrospective analysis of veterans who received pegylated interferon plus ribavirin at any VA medical facility (2001-2008).
SVR = sustained virological response.
SVR and All-cause Mortality in CHC Patients with Advanced Fibrosis

Baseline factors significantly associated with all-cause mortality:
• Older age
• GT 3 (2-fold increase in mortality and HCC)
• Higher Ishak fibrosis score
• Diabetes
• Severe alcohol use

530 patients followed for a median of 8.4 years

<table>
<thead>
<tr>
<th>Event</th>
<th>SVR patients</th>
<th>Non-SVR patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>8.9%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Liver-related mortality or liver transplant</td>
<td>1.9%</td>
<td>27.4%</td>
</tr>
<tr>
<td>HCC</td>
<td>5.1%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Liver failure</td>
<td>2.1%</td>
<td>29.9%</td>
</tr>
</tbody>
</table>

Highly Efficacious Treatments Are Not Enough

- All HCV patients: 100%
- Diagnosis and treatment: 20% success rate
- Cure: 10% success rate

Slide courtesy of Prof. Michael Manns
Summary

- HCV is the most dangerous infectious disease in America
- HCV is the leading cause of cirrhosis, HCC and liver transplantation in the US
- Unlike HBV and HIV...HCV can be cured
- Cure of HCV improves QOL & all cause mortality
- Current treatment is both safe, well tolerated, and highly effective
- We must continue to screen some patients for HCC after cure of HCV
- We must improve our efforts to screen for and treat this silent killer